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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,487	03/03/2006	Richard Edwards	ASZD-P01-135	7327

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EXAMINER	
DUTT, ADITI	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 10/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/565,487	EDWARDS ET AL.	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-20* is/are pending in the application.

4a) Of the above claim(s) *2,3,5-7,9,11-18 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8,10 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-3 and 5-20* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/20/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

1. The amendment of 20 January 2006 in the specification and claims has been entered in full. Claim 17 has been amended.

Election with traverse

2. Applicant's election with traverse of Group I, claims 1, 8,10 and 19, in the reply filed on 17 August 2006 is acknowledged.

3. The traversal is on the ground(s) that all the method claims 1-3 and 5-20, which include the non-elected Groups II-IX, encompassing claims 2-9, 11-18 and 20 could be searched and examined as a single discovery without undue burden as there was unity of invention, based on the PCT searching authority. This is not found persuasive because the groups lack the same or corresponding technical feature, as the prior art by Leung et al. (Jour Endocrinology 168: 497-508, 2001) teach a method of determining the modulation of OXTR mRNA expression using in situ hybridization using the same method steps as recited in claim 1 of the instant application (see page 499, sections "experimental explant culture treatments" and "in situ hybridization"; page 502, figure 2A).

4. Furthermore, the analytical methods of inventions I, II and IX have a special technical feature and are restricted properly, as they are they are practiced with materially different process steps for materially different purposes

and each requires a non-coextensive search because of different starting materials, process steps, and goals. Additionally, the defining compounds used in the methods of inventions III-VIII do not share a common structure or activity. Furthermore, each patent application is examined on its own merits. The invention that was deemed to have unity by the PCT searching authority has no bearing on the national stage application that follows US practice. Finally, the claims in the national stage application can be restricted on the basis of lack of unity of invention at the discretion of the examiner. See 37 CFR 1.499.

The requirement is still deemed proper and is therefore made FINAL.

5. Claims 2-3, 5-7, 9, 11-18 and 20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 17 August 2006.

6. Claims 1, 8, 10 and 19 drawn to a method of measuring oxytocin receptor (OXTR) nucleic acid expression are being considered for examination in the instant application.

Specification

7. The disclosure is objected to because of the following informalities:

Internet address:

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see, for example, page 5, para 2).

Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

8. Claim 10 is objected to because of the following informalities: Acronym "CAD" recited should be spelled out in all independent claims for clarity. Appropriate correction is required.

Claim Rejections - 35 USC § 112-Lack of Enablement

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 10 and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

11. The specification does not reasonably provide enablement for a method of determining OXTR gene expression using 'any' cell or 'any' sample from a subject or a CAD patient. The specification also does not reasonable provide

enablement for a method for diagnosis of CAD or determine susceptibility to CAD.

12. The claims are drawn to a method for determining the difference in OXTR gene/mRNA expression in a cell/sample from a CAD patient with that of a control cell (Claim 10); "a decrease or an increase" in the OXTR mRNA levels indicating a method for diagnosis or susceptibility of a subject to CAD (see claim 19). It is noted that the examiner has broadly interpreted the method for determining gene expression in "a cell" or "a sample" to encompass the expression in vivo, in vitro or in situ in "any" cell or "any" sample.

13. The specification of the instant application teaches that OXTR is a seven transmembrane G-protein coupled receptor that is encoded by a single gene and is located in chromosome region 3p (page 5, para 1, 2). The specification further teaches that OXTR is expressed in the cardiovascular system (endothelial cells from the aorta and other vessels), and is involved in the regulation of the vascular tone, cardiac rate and contraction (page 5, para 1). Furthermore, the specification only demonstrates polymorphisms in the OXTR gene in CAD affected sibling pairs, thereby asserting an association of OXTR with CAD (page 35-40, examples 1 and 2). The specification also does not teach that differential expression of the OXTR gene is associated with CAD. Undue experimentation would be required by the skilled artisan to determine such. Neither the specification nor the examples teach any clear nexus of OXTR gene expression in all possible samples or all possible cell types, and susceptibility to CAD or the

diagnosis of CAD. A large quantity of experimentation would be required by one skilled in the art to determine the magnitude of OXTR gene expression in all possible samples and cell types and then diagnose CAD or a susceptibility thereto in a subject. Such experimentation is considered undue.

14. Relevant literature teaches that oxytocin receptor gene is localized in a gamut of tissues and cells such as the brain, thymus, adrenal gland, breast, reproductive organs, aorta and other blood vessels, endothelial cells and adipocytes (Gimpl and Fahrenholz, Physiol Rev 81: 629-683, 2001, pages 645-659, Table 3 and 4; Jankowski et al. PNAS 97: 6207-6211, 2000, figure 5). Relevant art also discloses that OXTR mRNA concentration in the heart is about 10 times lower than that present in the uterus of a nonpregnant rat (Gimpl, page 652, para 1) and that higher concentrations are observed in the atrium than in the ventricles. The art further teaches that oxytocin induces the release of atrial natriuretic peptide (ANP) from perfused rat heart by oxytocin receptor activation, an action that is inhibited by oxytocin receptor antagonist (Gutkowska et al., Brazilian J of Med and Biol Research 33: 625-633, 2000, page 629, column 2, para 2; page 630, last para; Gutkowska et al. PNAS 94: 11704-11709, 1997). However, as suggested by Miller et al. (Amer J Physiol Heart Circ Physiol. 282: H1223-H1228, 2002), despite the presence of OXTR mRNA in the rat aorta, the direct physiological role of OXTR on the vascular tone remains unclear and unknown (page H1226, last 2 paras). Furthermore, the literature and instant specification do not teach the difference in OXTR gene/mRNA expression in a

cell or a sample, in vivo or in vitro, in a subject having CAD from that of a control. The specification or relevant art also does not teach the susceptibility or diagnosis of CAD by measuring OXTR gene expression in all possible cell types or samples. Due to breadth of the claims and the absence of working examples indicating the gene expression of OXTR for determining the susceptibility to CAD or for diagnosis of CAD, undue experimentation would be required of the skilled artisan.

15. The Examiner has noted that single nucleotide polymorphism in CAD affected subjects do not necessarily reflect changes in mRNA expression. As suggested by Wang et al (The AAPS Journal 8: E515-E520, 2006) on the relationship of mRNA levels and polymorphism, that although reporter gene assays revealed useful information about polymorphism, "failed to reveal how a polymorphism affects expression in the physiological target tissue" (page E515, column 2, para 2), and cautions against relying on SNP information for correlation with mRNA levels (page E518 and E519, column 1 para 2). Thus based upon the state of the prior art and the instant specification, the skilled artisan would not be able to necessarily predict that by measuring a change in OXTR gene expression in a cell or a sample one would be able to determine the diagnosis or susceptibility to CAD. Additionally, as observed in the literature, different cells and tissues will have different concentrations of OXTR mRNA and also elicit varied responses to different stimuli and disease states. The instant

specification has provided little guidance as to a clear nexus between OXTR gene expression and CAD in any cell or any sample.

16. Due to the large quantity of experimentation necessary to identify all possible cells or samples that have normal/abnormal OXTR gene expression, and to determine that differential expression of the OXTR gene is associated with CAD or susceptibility to CAD in vivo or in vitro; the lack of direction/guidance presented in the specification regarding the same; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which has yet to identify a single gene associated with CAD; and the unpredictability of determining a nexus between OXTR gene expression and CAD, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112, first paragraph- Written Description

17. Claims 1, 8, 10 and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

18. The claims are drawn to identifying a test compound that modulates the gene expression of OXTR by contacting 'any' cell capable of expressing OXTR gene (see claim 1) and formulating the compound in a pharmaceutical

composition (see claim 8). Furthermore, the claims are drawn to a method for determining the difference in OXTR gene/mRNA expression in 'any' cell from a CAD patient with that of a control cell (Claim 10); "a decrease or an increase" in the OXTR mRNA levels in 'any' sample, as compared to a control sample, indicating a method for diagnosis or susceptibility of a subject to CAD (see claim 19).

19. The specification of the instant application teaches that OXTR is a seven membrane G protein coupled receptor that is encoded by a single gene and is located in chromosome region 3P (page 5, para 1, 2). The specification further teaches that OXTR is expressed in the cardiovascular system (endothelial cells from the aorta and other vessels), and is involved in the regulation of the vascular tone, cardiac rate and contraction (page 5, para 1). Furthermore, the specification demonstrates polymorphisms in the OXTR gene in CAD affected sibling pairs, thereby asserting an association of OXTR polymorphisms with CAD (page 35-40, examples 1 and 2). However, the brief description in the specification of one example of blood sample and cells, is not adequate written description of an entire genus of methods encompassing a genus of samples and a genus of cells. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of specific physiological characteristics, physical and/or chemical properties, functional features, structure/function correlation, or

any combination thereof. However, in this case, the specification has not shown a relationship between the claimed genus of cells or samples and OXTR gene expression.

20. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

21. The skilled artisan cannot envision the genus of cells or samples, of the encompassed methods, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

22. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class.

23. Therefore, only methods of utilizing a blood sample, or specific cell type, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear

that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

24. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

25. Claim 1 is rejected under 35 U.S.C. 102(b) as clearly anticipated by Leung et al. (Jour Endocrinology 168: 497-508, 2001).

26. Leung et al teach a method of determining the modulation of OXTR mRNA expression using in situ hybridization, comprising incubating bovine endometrial explants in the presence or absence of different compounds, for example lipopolysaccharide, dexamethasone or both, thereafter determining an increase or decrease in the OXTR mRNA expression by the compounds as compared to

that observed in the absence of the test compounds in the control group (see page 499, sections "experimental explant culture treatments" and "in situ hybridization"; page 502, figure 2A). Because the method steps disclosed by Leung et al meets the limitations of claim 1 of the instant application, the method described in the reference anticipates the invention.

27. Claims 1 and 8 are rejected under 35 U.S.C. 102(a) and 102(e) as clearly anticipated by Golz et al. (International Publication No. WO 03/093816, published 13 November 2003; filed 28 April 2003).

28. Golz et al. teach a screening assay, wherein a cell capable of expressing OXTR is contacted with a candidate compound; the level of increase or decrease of OXTR mRNA expression in the presence of the candidate compound is determined as compared to that in its absence, thereby identifying the candidate compound as a regulator of OXTR expression (page 45, lines 5-19). Golz et al. also teaches that the identified regulator may be prepared into a pharmaceutical composition (page 67, lines 10-31). Because the method steps disclosed by Golz et al meet the limitations of claims 1 and 8 of the instant application, the method described in the reference anticipates the invention.

Conclusion

29. No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Jankowski et al. PNAS 101: 13074-13079, 2004.

(Reference showing the ontogeny of OXTR in rat cardiomyocytes)

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

31. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

32. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-

direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
September 22, 2006

Bridget E. Bunner

BRIDGET BUNNER
PATENT EXAMINER